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Facile synthesis of chelating bisphosphine oxides and bisphosphines via palladium-catalyzed bishydrophosphinylation reactions

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Abstract—A series of functional bisphosphophosphine oxides were synthesized in good yields via new Pd-catalyzed bis-hydrophosphinylation reactions of terminal alkynes and diphenylphosphine oxide. The resulting bisphosphine oxides were reduced to their corresponding bisphosphines in quantitative yields via a $Ti(O^iPr)_4$-mediated process.

Bisphosphineoxides are an important class of materials because of their applications as organoextractants in hydrometallurgy and as fire retardants.[1] Their reduced products, bisphosphines, are important ancillary ligands in organometallic chemistry and homogeneous catalysis.[2] In particular, chiral phosphines have been successfully employed in many enantioselective catalytic processes including asymmetric hydrogenation, hydrosilation, hydroformylation and hydrovinylation reactions.[3] Most chiral bisphosphines have been derived from naturally occurring chiral pools with the notable exception of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.[4] Synthetic elaboration from naturally occurring chiral pools is limited in scope, and it would be desirable to develop alternative methodologies for the facile and economical synthesis of a wide variety of chiral chelating bisphosphines as ancillary ligands for transition-metal mediated asymmetric catalysis. Herein we wish to report a new Pd-catalyzed bis-hydrophosphinylation reaction of terminal alkynes to afford chelating bisphosphineoxides and their reduction to bisphosphines via a Ti-mediated process.

Terminal alkynes were either obtained from commercial sources or synthesized in excellent yields by Heck reactions between aryl halides and trimethysilylacetylene followed by removal of trimethylsilyl group under basic conditions.[5] Treatment of 2-ethynyl pyridine with 3 equiv. of diphenylphosphine oxide in the presence of 5 mol% $Pd(PPh_3)_4$ in refluxing toluene over a period of 24 h afforded the *vicinal*-bisphosphophosphine oxide **1** in 90% yield (Scheme 1).[6] This new bis-hydrophosphinylation reaction can be applied to various aliphatic and aromatic terminal alkynes containing electronically neutral, electron-withdrawing, and electron-donating functionalities. The resulting bis-diphenylphosphine oxides **1**–**11** have been characterized by ^1H, $^1H\{^{31}P\}$, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectroscopy and high resolution mass spectrometry.[7] The characteristic signals for the protons on the alkane backbone of **1** appear as three distinct multiplets at $\sim\delta$ 4.6–2.8, which collapse into a doublet, a doublet of doublets, and a doublet upon decoupling the ^{31}P nuclei. The fact that the other *vicinal* $^3J_{H-H}$ is negligible is consistent with the *anti* conformation of the two *vicinal* diphenylphosphine oxide groups. The aromatic protons on the phenyl ring appear as several complex multiplets because of their diastereotopic nature. The $^{31}P\{^1H\}$ NMR spectra of these *vicinal* bis-diphenylphosphine oxides appear as two doublets at $\sim\delta$ 33 and $\sim\delta$ 30 with a $^3J_{P-P}$ of $\sim$44 Hz. The carbons of the alkane backbone appear as two sets of doublets of doublets in the $^{13}C\{^1H\}$ NMR spectrum.

When the hydrophosphinylation reactions were carried out with 1 equiv. of diphenylphosphine oxide under milder conditions and shorter reaction times, both *geminal* alkenyl diphenylphosphine oxide and terminal alkenyl diphenylphosphine oxide were isolated. Both *geminal*- and *terminal*-alkenyl diphenylphosphine oxides readily undergo the second hydrophosphinylation reaction to result in *vicinal*-bisphosphineoxides.

Keywords: catalysis; palladium; titanium; phosphine oxides; phosphines.

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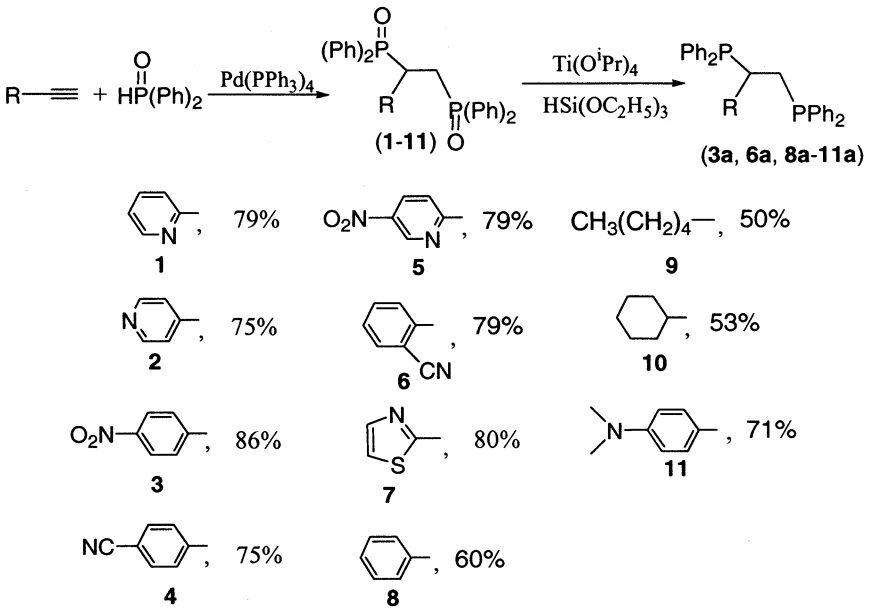

Scheme 1.

We thus believe that the bis-hydrophosphinylation reaction proceeds via oxidative addition of diphenylphosphine oxide to a Pd(0) catalyst followed by insertion of alkynes into the Pd–H bond to afford both regioisomers of alkenylpalladium intermediates,[8] which undergo reductive elimination to afford both geminal- and terminal-alkenyl diphenylphosphine oxides and regenerate the active Pd(0) catalyst. Subsequent hydrophosphinylation with alkenyl diphenylphosphine oxides as the substrates lead to bis-diphenylphosphine oxides **1**–**11**.

Reduction of phosphine oxides is typically carried out with a metal hydride system or with $HSiCl_3$ in the presence of a base. We have tried both procedures and only obtained products resulting from P–C bond cleavage. We have successfully reduced bis-diphenylphosphine oxides to their corresponding b2isphosphines by employing the triethoxysilane and $Ti(O^iPr)_4$ system first developed by Lawrence et. al.[9] and Buchwald et al.[10]

Treatment of vicinal-bisphosphineoxides **3**, **6**, and **8**–**11** with 6 equiv. of triethoxysilane and a catalytic amount of $Ti(O^iPr)_4$ in refluxing toluene afforded their corresponding bisphosphines in quantitative yields after column chromatography. The reaction proceeds rapidly and is complete in 5–20 min for the substrates studied.[11,12]

The characteristic signals for the protons on the alkane backbone of **11a** appear as three distinct multiplets at δ 3.22–2.44. Upon decoupling the ^{31}P nuclei, these three proton signals collapse into a doublet at δ 3.21 and a multiplet at $\sim\delta$ 2.5. As expected, the $^{31}P\{^1H\}$ NMR spectra of these vicinal bis-diphenylphosphines appear as two sets of doublets. The $^{13}C\{^1H\}$ NMR spectrum of **11a** shows the aromatic carbons as a complex series of multiplets between δ 150–115. The carbons of the alkane backbone appear as a triplet and two sets of doublets of doublets.

In summary, we have developed an efficient method for the synthesis of functional bis-diphenylphosphine oxides via Pd-catalyzed bis-hydrophosphinylation reactions of alkynes with diphenylphosphine oxide. We have also shown the facile reduction of the bisphosphine-oxides to the corresponding bisphosphines using triethoxysilane/$Ti(O^iPr)_4$.

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6. **A typical procedure for bis-hydrophosphinylation reactions of terminal alkynes**: To a mixture of 2-ethynyl pyridine (100 mg, 0.97 mmol), diphenylphosphine oxide (490 mg, 2.4 mmol), and $Pd(PPh_3)_4$ (39 mg, 5 mol%) was added 3 mL of anhydrous toluene under nitrogen. The dark

brown solution was heated to reflux and a solid began to precipitate out of solution about 30 min later. The reaction was stopped after 20 h, cooled to rt, and the solvent was removed under reduced pressure. The resulting solid was washed with diethyl ether (3×15 mL) to afford 390 mg of pure 1-(2′-pyridyl)-1,2-bis(diphenylphosphinyl)-ethane, **1** as a white solid (yield: 79%).

7. Selected data for new vicinal bis-diphenylphosphine oxides: All the spectra were taken in $CDCl_3$ at 400 MHz for ^1H, 125 MHz for ^{13}C, and 161 MHz for ^{31}P nucleus, respectively. **3**, **8**, **9**, and **11** are known compounds.

Compound 1: mp 219–221°C; ^1H NMR: δ 8.16 (d, 1H, $J=4.3$ Hz), 7.94–7.89 (m, 2H), 7.59–7.31 (m, 12H), 7.27–7.23 (m, 1H), 7.17–7.13 (m, 3H), 7.08–7.02 (m, 2H), 6.80 (d, 1H, $J=7.9$ Hz), 6.73–6.70 (m, 1H), 4.51–4.43 (m, 1H), 3.36–3.54 (m, 1H), 2.90–2.75 (m, 1H); ^{13}C NMR: δ 154.3, 148.9, 135.3, 132.0 131.7–131.4 (m), 131.2–130.7 (m), 130.4 (d, $J_{C-P}=9.2$ Hz), 128.9 (d, $J_{C-P}=11.4$ Hz), 128.6 (d, $J_{C-P}=11.4$ Hz), 127.9 (t, $J_{C-P}=10.7$ Hz), 41.9 (d, $J_{C-P}=63.3$ Hz), 28.3 (d, $J_{C-P}=68.7$ Hz); ^{31}P NMR: δ 35.5 (d, $J_{P-P}=46.1$ Hz), 31.2 (d, $J_{P-P}=46.1$ Hz). HRMS (EI) calcd for $C_{31}H_{28}NO_2P_2$ (MH^+), 508.1595; found, 508.1593.

Compound 2: mp 264–266°C; ^1H NMR: δ 8.04–8.00 (m, 1H), 7.57–6.95 (m, 23H), 4.26–4.18 (m, 1H), 3.12–3.04 (m, 1H), 2.87–2.77 (m, 1H); ^{13}C NMR: δ 141.1, 132.7, 132.2, 132.0, 131.9, 131.7 (d, $J_{C-P}=8.4$ Hz), 131.0–130.8 (m), 130.4 (d, $J_{C-P}=9.9$ Hz), 129.5 (d, $J_{C-P}=11.4$ Hz), 129.0 (d, $J_{C-P}=11.4$ Hz), 128.4 (t, $J_{C-P}=12.2$ Hz), 39.4 (d, $J_{C-P}=68.8$ Hz), 29.8 (d, $J_{C-P}=68.8$ Hz); ^{31}P NMR: δ 35.4 (d, $J_{P-P}=44.7$ Hz), 29.8 (d, $J_{P-P}=44.7$ Hz). HRMS(EI) calcd for $C_{31}H_{28}NO_2P_2$ (MH^+), 508.1595; found, 508.1591.

Compound 4: mp 308–310°C; ^1H NMR: δ 8.03–8.01 (m, 2H), 7.57–7.50 (m, 5H), 7.47–7.44 (m, 1H), 7.39–7.35 (m, 2H), 7.33 (m, 6H), 7.20–7.16 (m, 4H), 7.11–7.06 (m, 4H), 4.34–4.28 (m, 1H), 3.14–3.05 (m, 1H), 2.86–2.76 (m, 1H); ^{13}C NMR: δ 140.2, 132.5, 132.0, 131.8, 131.7, 131.4, 131.3, 130.8–130.5 (m), 130.1 (d, $J_{C-P}=9.2$ Hz), 129.2 (d, $J_{C-P}=12.2$ Hz), 129.3 (d, $J_{C-P}=11.4$ Hz), 128.2 (d, $J_{C-P}=12.2$ Hz), 128.1 (d, $J_{C-P}=11.4$ Hz), 118.5, 110.6, 39.8 (d, $J_{C-P}=65.3$ Hz), 29.8 (d, $J_{C-P}=65.3$ Hz); ^{31}P NMR: δ 35.3 (d, $J_{P-P}=45.4$ Hz), 29.9 (d, $J_{P-P}=45.4$ Hz). HRMS(EI) calcd for $C_{33}H_{28}NO_2P_2$ (MH^+), 532.1595; found, 532.1597.

Compound 5: mp 254–255°C; ^1H NMR: δ 8.93 (d, 1H $J=2.4$ Hz), 7.96–7.88 (m, 2H), 7.63–7.42 (m, 15H), 7.40–7.35 (m, 3H), 7.28–7.12 (m, 2H), 4.70–4.36 (m, 1H), 3.62–3.53 (m, 1H), 2.89–2.79 (m, 1H); ^{13}C NMR: δ 144.3, 132.7 (d, $J_{C-P}=2.4$ Hz), 132.3, 131.9, 131.7 (d, $J_{C-P}=8.4$ Hz), 131.6 (d, $J_{C-P}=2.3$ Hz), 131.2 (t, $J_{C-P}=8.4$ Hz), 130.7 (d, $J_{C-P}=9.2$ Hz), 130.3, 129.4 (d, $J_{C-P}=11.4$ Hz), 129.0 (d, $J_{C-P}=12.2$ Hz), 128.6 (d, $J_{C-P}=11.4$ Hz), 128.3 (d, $J_{C-P}=12.2$ Hz), 125.3 (d, $J_{C-P}=3.8$ Hz), 43.0 (d, $J_{C-P}=62.6$ Hz), 28.9 (d, $J_{C-P}=69.4$ Hz); ^{31}P NMR: δ 33.9 (d, $J_{P-P}=44.3$ Hz), 29.9 (d, $J_{P-P}=44.3$ Hz). HRMS(EI) calcd for $C_{31}H_{27}N_2O_4P_2$ (MH^+), 553.1446; found, 553.1447.

Compound 6: mp 258–259°C; ^1H NMR: δ 7.94–7.89 (m, 2H), 7.82 (d, 11H $J=8.5$ Hz), 7.64–7.58 (m, 3H), 7.55–7.48 (m, 4H), 7.47–7.41 (m, 4H), 7.37 (s, 1H), 7.36–7.26 (m, 5H), 7.24–7.14 (m, 4H), 7.09–7.05 (m, 1H), 4.60–4.51 (m, 1H), 3.28–3.18 (m, 1H), 2.85–2.75 (m, 1H); ^{13}C NMR: δ 132.7, 132.5, 132.4, 132.2, 132.0 (d, $J_{C-P}=3.1$ Hz), 131.7, 131.6, 131.1 (d, $J_{C-P}=3.1$ Hz), 131.0 (d, $J_{C-P}=3.1$ Hz), 130.8 (d, $J_{C-P}=9.2$ Hz), 129.9 (d, $J_{C-P}=11.4$ Hz), 129.0 (d, $J_{C-P}=11.4$ Hz), 128.5 (d, $J_{C-P}=12.2$ Hz), 128.3 (d, $J_{C-P}=12.2$ Hz), 127.6, 117.7, 37.9 (d, $J_{C-P}=63.3$ Hz), 30.3 (d, $J_{C-P}=68.7$ Hz); ^{31}P NMR: δ 34.9 (d, $J_{P-P}=45.4$ Hz), 29.1 (d, $J_{P-P}=46.1$ Hz). HRMS(EI) calcd for $C_{33}H_{28}NO_2P_2$ (MH^+), 532.1595; found, 532.1589.

Compound 7: mp 197–199°C; ^1H NMR: δ 7.99–7.94 (m, 2H), 7.63–7.51 (m, 11H), 7.49–7.34 (m, 4H), 7.30–7.24 (m, 2H), 7.21–7.17 (m, 2H), 6.85 (d, 1H, $J=3.1$ Hz), 4.92–4.84 (m, 1H), 3.54–3.46 (m, 1H), 2.96–2.86 (m, 1H); ^{13}C NMR: δ 165.2, 142.4 (d, $J_{C-P}=2.3$ Hz), 132.6 (d, $J_{C-P}=2.3$ Hz), 132.1 (t, $J_{C-P}=3.1$ Hz), 131.8 (d, $J_{C-P}=8.4$ Hz), 131.5 (d, $J_{C-P}=9.2$ Hz), 131.4, 131.2 (d, $J_{C-P}=9.9$ Hz), 130.6 (d, $J_{C-P}=9.9$ Hz), 129.3 (d, $J_{C-P}=12.3$ Hz), 128.9 (d, $J_{C-P}=11.4$ Hz), 128.5 (d, $J_{C-P}=12.2$ Hz), 128.3 (d, $J_{C-P}=12.2$ Hz), 120.2, 38.8 (d, $J_{C-P}=62.2$ Hz), 30.1 (d, $J_{C-P}=67.9$ Hz); ^{31}P NMR: δ 33.6 (d, $J_{P-P}=41.0$ Hz), 30.3 (d, $J_{P-P}=41.0$ Hz). HRMS(EI) calcd for $C_{29}H_{25}NO_2P_2S$ (M^+), 513.1081; found, 513.1075.

Compound 10: mp 239–241°C; ^1H NMR: δ 7.80–7.67 (m, 5H), 7.56–7.26 (m, 15H), 3.08–2.93 (m), 2.68–2.51 (m), 1.68–1.60 (m), 1.55–1.43 (m), 0.88–0.72 (m); ^{13}C NMR: δ 131.6 (d, $J_{C-P}=2.3$ Hz), 131.4 (d, $J_{C-P}=3.1$ Hz), 131.3, 130.9 (d, $J_{C-P}=8.4$ Hz), 130.8 (d, $J_{C-P}=8.4$ Hz), 130.6 (d, $J_{C-P}=9.2$ Hz), 130.5 (d, $J_{C-P}=9.2$ Hz), 128.6 (d, $J_{C-P}=3.8$ Hz), 128.5, 128.4, 128.3 (d, $J_{C-P}=2.3$ Hz), 38.2, 36.9, 36.3, 31.7 (d, $J_{C-P}=9.9$ Hz), 30.6, 26.7 (d, $J_{C-P}=17.5$ Hz), 25.7, 25.1, 24.4; ^{31}P NMR: δ 37.8 (d, $J_{P-P}=42.6$ Hz), 30.9 (d, $J_{P-P}=42.6$ Hz). HRMS(EI) calcd for $C_{32}H_{35}O_2P_2$ (MH^+), 513.2112; found, 513.2110.

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11. **A typical procedure for the reduction of bis-diphenylphosphine oxides**: To a mixture of **11** (200 mg, 0.36 mmol), titanium isopropoxide (60 μL, 0.2 mmol) and triethoxy silane (354 μL, 2.16 mmol) was added 5 mL of anhydrous benzene under nitrogen. The pale brown slurry was heated to reflux, and the solid dissolved and the solution turned gray–green 25 min later. The reaction was stopped, cooled to rt and the solvent was removed in vacuo to afford a brown solid. The crude material was purified by column chromatography under nitrogen (degassed $CHCl_3$/acetone 2:1) to afford 195 mg (98%) of 1-(4′-*N*,*N*-dimethylaminophenyl)-1,2-bis(diphenylphosphino)ethane, **11a**, as white solid.
12. Selected data for new vicinal bis-diphenylphosphines. **8a**–**10a** are known compounds.

Compound 3a. ^1H NMR: δ 7.98–7.96 (m, 1H), 7.82–7.80 (m, 1H), 7.92–7.66 (m, 5H), 7.64–7.33 (m, 8H), 7.23–6.97 (m, 10H), 4.27–4.06 (m, 1H), 2.85–2.72 (m, 2H); ^{13}C NMR: δ 132.5, 131.8, 131.62 (d, $J_{C-P}=19.3$ Hz), 131.5, 131.0 130.7–130.6 (m) 130.2 (d, $J_{C-P}=9.2$ Hz), 128.9 (d,

$J_{C-P}=10.7$ Hz), 128.5 (d, $J_{C-P}=12.2$ Hz), 127.9, 127.8, 40.6, 39.3 (d, $J_{C-P}=70.0$ Hz), 31.3 (d, $J_{C-P}=70.0$ Hz); ^{31}P NMR: δ 29.8 (d, $J_{P-P}=41.5$ Hz), 5.85 (d, $J_{P-P}=41.5$ Hz). HRMS(EI) calcd for $C_{32}H_{28}NO_2P_2$ (MH^+), 520.1595; found, 520.1602.

Compound 6a. ^{1}H NMR: δ 8.01 (d, 1H, $J=7.90$ Hz), 7.65–7.51 (m, 5H), 7.45–7.39 (m, 3H), 7.37–7.35 (m, 2H), 7.31–7.27 (m, 2H), 7.25–7.23 (m, 1H), 7.22–7.18 (m, 5H), 7.15–7.12 (m, 5H), 3.95–3.87 (m, 1H), 2 95–2.85 (m, 1H), 2.64–2.57 (m, 1H); ^{13}C NMR: δ 139.9, 137.9 (d, $J_{C-P}=$ 12.2 Hz), 136.2 (d, $J_{C-P}=15.2$ Hz), 134.3 (d, $J_{C-P}=20.6$ Hz), 133.0 (d, $J_{C-P}=2.3$ Hz), 132.2, 132.1, 131.7 (d, $J_{C-P}=17.5$ Hz), 131.6 (d, $J_{C-P}=3.1$ Hz), 131.2 (d, $J_{C-P}=$ 8.5 Hz), 130.7 (d, $J_{C-P}=9.2$ Hz), 129.8, 129.7, 128.8 (t, $J_{C-P}=11.4$ Hz), 128.3, 128.2, 128.0 (d, $J_{C-P}=12.2$ Hz), 127.5 7 (d, $J_{C-P}=2.3$ Hz), 117.6 (d, $J_{C-P}=1.5$ Hz), 114.1 7 (d, $J_{C-P}=6.1$ Hz), 41.3 (d, $J_{C-P}=16.8$ Hz), 40.5 (d, $J_{C-P}=16.8$ Hz), 29.3 (d, $J_{C-P}=16.8$ Hz); ^{31}P NMR: δ 35.3 (d, $J_{P-P}=31.7$ Hz), −17.9 (d, $J_{P-P}=31.7$ Hz). HRMS(EI) calcd for $C_{33}H_{28}NP_2$ (MH^+), 500.1697; found, 500.1688.

Compound 11a: ^{1}H NMR: δ 7.42–7.20 (m, 11H), 7.18 (d, 4H $J=3.1$ Hz) 7.42–7.23 (m, 8H), 7.16–7.12 (m, 4H), 7.08–7.03 (m, 2H), 6.91 (d, 2H $J=7.9$ Hz), 6.18 (d, 2H $J=7.9$ Hz), 4.20–4.12 (m, 1H), 3.12–3.03 (m, 1H), 2.80–2.70 (m, 7H); ^{13}C NMR: δ 149.6, 131.8, 131.6, 131.5, 131.0, 130.7–130.6 (m) 130.2 (d, $J_{C-P}=9.2$ Hz), 128.9 (d, $J_{C-P}=10.7$ Hz), 128.5 (d, $J_{C-P}=12.2$ Hz), 127.9, 127.8, 127.7, 40.6, 38.3 (d, $J_{C-P}=70.0$ Hz), 30.3 (d, $J_{C-P}=70.0$ Hz); ^{31}P NMR: δ 35.9 (d, $J_{P-P}=48.8$ Hz), 30.9 (d, $J_{P-P}=48.8$ Hz). HRMS(EI) calcd for $C_{34}H_{34}NP_2$ (MH^+), 518.2166; found, 518.2162.